Amendments to the Claims

This listing of claims replaces all prior versions and listings of claims in the application.

Listing of Claims

1. (Currently Amended) An isolated nucleic acid molecule ~~comprising~~ consisting essentially of a *PNMT* nucleic acid sequence~~, wherein said nucleic acid molecule is at least ten nucleotides in length, and wherein said *PNMT* nucleic acid sequence comprises a nucleotide sequence variant at a position~~ selected from the group consisting of:

a) at least ten contiguous nucleotides of SEQ ID NO:6, wherein said sequence includes nucleotide ~~position~~ 32, 159, 298, 340, or 462 of SEQ ID NO:6, with the proviso that the nucleotide at position 32 is guanine, the nucleotide at position 159 is thymine, the nucleotide at position 298 is guanine, the nucleotide at position 340 is thymine, or the nucleotide at position 462 is guanine;

b) ~~position 1, 360, 616, or 757 relative to the guanine in the splice donor site of intron 1 within~~ at least ten contiguous nucleotides of SEQ ID NO:1, wherein said sequence includes nucleotide 1895, 2254, 2510, or 2651 of SEQ ID NO:1, with the proviso that the nucleotide at position 1895 is thymine, the nucleotide at position 2254 is cytosine, the nucleotide at position 2510 is adenine, or the nucleotide at position 2651 is adenine;

c) ~~position 940 or 941 relative to the adenine in the *PNMT* translation initiation codon within~~ at least ten contiguous nucleotides of SEQ ID NO:1, wherein said sequence includes nucleotide 3692 or 3693 of SEQ ID NO:1, with the proviso that the nucleotide at position 3692 is thymine or the nucleotide at position 3693 is adenine; ~~and~~

d) ~~position -591, -392, -390, -229, or -184 relative to the adenine in the *PNMT* translation initiation codon within~~ at least ten contiguous nucleotides of SEQ ID NO:1, wherein said sequence includes nucleotide 1102, 1301, 1303, 1464, or 1509 of SEQ ID NO:1, with the proviso that the nucleotide at position 1102 is thymine, the nucleotide at position 1301 is cytosine, the nucleotide at position 1303 is adenine, the nucleotide at position 1464 is adenine, or the nucleotide at position 1509 is adenine; and

e) the complement of a), b), c), or d).

2. (Canceled)

3. (Currently Amended) The isolated nucleic acid molecule of claim 1, wherein said nucleotide sequence ~~variant~~ is ~~a thymine substitution for cytosine at position 940 relative to the adenine in the *PNMT* translation initiation codon, or an adenine substitution for guanine at position 941 relative to the adenine in the *PNMT* translation initiation codon~~ at least ten contiguous nucleotides of SEQ ID NO:1, wherein said sequence includes nucleotide 3692 or 3693 of SEQ ID NO:1, with the proviso that the nucleotide at position 3692 is thymine or the nucleotide at position 3693 is adenine.

4. (Currently Amended) The isolated nucleic acid molecule of claim 1, wherein said nucleotide sequence ~~variant~~ is ~~a thymine substitution for guanine at position 1 relative to the guanine in the splice donor site of intron 1, a cytosine substitution for thymine at position 360 relative to the guanine in the splice donor site of intron 1, an adenine substitution for guanine at position 616 relative to the guanine in the splice donor site of intron 1, or an adenine substitution for cytosine at position 757 relative to the guanine in the splice donor site of intron 1~~ at least ten contiguous nucleotides of SEQ ID NO:1, wherein said sequence includes nucleotide 1895, 2254, 2510, or 2651 of SEQ ID NO:1, with the proviso that the nucleotide at position 1895 is thymine, the nucleotide at position 2254 is cytosine, the nucleotide at position 2510 is adenine, or the nucleotide at position 2651 is adenine.

5. (Currently Amended) The isolated nucleic acid molecule of claim 1, wherein said nucleotide sequence ~~variant~~ is ~~a thymine substitution for guanine at position -591 relative to the adenine in the *PNMT* translation initiation codon within SEQ ID NO:1, a cytosine substitution for guanine at position -392 relative to the adenine in the *PNMT* translation initiation codon within SEQ ID NO:1, an adenine substitution for guanine at position -390 relative to the adenine in the *PNMT* translation initiation codon within SEQ ID NO:1, an adenine substitution for guanine at position -229 relative to the adenine in the *PNMT* translation initiation codon within SEQ ID NO:1, or an adenine substitution for~~

~~guanine at position -184 relative to the adenine in the *PNMT* translation initiation codon within SEQ ID NO:1~~ at least ten contiguous nucleotides of SEQ ID NO:1, wherein said sequence includes nucleotide 1102, 1301, 1303, 1464, or 1509 of SEQ ID NO:1, with the proviso that the nucleotide at position 1102 is thymine, the nucleotide at position 1301 is cytosine, the nucleotide at position 1303 is adenine, the nucleotide at position 1464 is adenine, or the nucleotide at position 1509 is adenine.

6. (Currently Amended) The isolated nucleic acid molecule of claim 1, wherein said nucleotide sequence ~~variant~~ is at least ten contiguous nucleotides of SEQ ID NO:6, wherein said sequence includes nucleotide 32 of SEQ ID NO:6, with the proviso that the nucleotide at position 32 of SEQ ID NO:6 is [[a]] guanine ~~substitution for adenine~~.

7. (Currently Amended) The isolated nucleic acid molecule of claim 1, wherein said nucleotide sequence ~~variant~~ is at least ten contiguous nucleotides of SEQ ID NO:6, wherein said sequence includes nucleotide159 of SEQ ID NO:6, with the proviso that the nucleotide at position 159 of SEQ ID NO:6 is [[a]] thymine ~~substitution for cytosine~~.

8. (Currently Amended) The isolated nucleic acid molecule of claim 1, wherein said nucleotide sequence ~~variant~~ is at least ten contiguous nucleotides of SEQ ID NO:6, wherein said sequence includes nucleotide 298 of SEQ ID NO:6, with the proviso that the nucleotide at position 298 of SEQ ID NO:6 is [[a]] guanine ~~substitution for adenine~~.

9. (Currently Amended) The isolated nucleic acid molecule of claim 1, wherein said nucleotide sequence ~~variant~~ is at least ten contiguous nucleotides of SEQ ID NO:6, wherein said sequence includes nucleotide 340 of SEQ ID NO:6, with the proviso that the nucleotide at position 340 of SEQ ID NO:6 is [[a]] thymine ~~substitution for cytosine~~.

10. (Currently Amended) The isolated nucleic acid molecule of claim 1, wherein said nucleotide sequence ~~variant~~ is at least ten contiguous nucleotides of SEQ ID NO:6, wherein said sequence includes nucleotide 462 of SEQ ID NO:6, with the proviso that the nucleotide at position 462 of SEQ ID NO:6 is [[a]] guanine ~~substitution for adenine~~.

11. (Original) An isolated nucleic acid encoding a PNMT polypeptide, wherein said polypeptide comprises a PNMT amino acid sequence variant relative to the amino acid sequence of SEQ ID NO:8, and wherein said amino acid sequence variant is at a residue selected from the group consisting of 9, 98, and 112.

12. (Original) The isolated nucleic acid of claim 11, wherein said amino acid sequence variant is a serine at residue 9, an alanine at residue 98, or a cysteine at residue 112.

13. (Withdrawn) An isolated PNMT polypeptide, wherein said polypeptide comprises a PNMT amino acid sequence variant relative to the amino acid sequence of SEQ ID NO:8, wherein said amino acid sequence variant is at a residue selected from the group consisting of 9, 98, and 112.

14. (Withdrawn) The isolated polypeptide of claim 13, wherein said amino acid sequence variant is a serine at residue 9, an alanine at residue 98, or a cysteine at residue 112.

15. (Withdrawn) The isolated polypeptide of claim 13, wherein activity of said polypeptide is altered relative to a wild type PNMT polypeptide.

16. (Canceled)

17. (Withdrawn) A method for determining if a subject is predisposed to a disease, wherein said method comprises:

a) obtaining a biological sample from said mammal, and

b) detecting the presence or absence of a *PNMT* nucleotide sequence variant in said sample, wherein predisposition to said disease is determined based on the presence or absence of said variant.

18. (Withdrawn) The method of claim 17, wherein said method further comprises detecting the presence or absence of a plurality of said *PNMT* nucleotide sequence variants in said sample to obtain a variant profile of said subject, and wherein predisposition to said disease is determined based on said variant profile.

19. (Withdrawn) The method of claim 18, wherein said disease is a multiple sclerosis.

20. (Withdrawn) The method of claim 18, wherein said disease is early onset Alzheimer's disease.

21. (Withdrawn) A method for assisting a medical or research professional, wherein said method comprises:

a) obtaining a biological sample from a subject, and

b) detecting the presence or absence of a plurality of *PNMT* nucleotide sequence variants in said sample to obtain a variant profile of said subject.

22. (Withdrawn) The method of claim 21, wherein said method further comprises communicating said profile to said medical or research professional.

23. (Withdrawn) A method for determining the methyltransferase status of an individual, said method comprising determining whether said subject comprises a variant *PNMT* nucleic acid.

24. (Withdrawn) A method for predicting the therapeutic efficacy of a compound in a subject, wherein metabolism of said compound comprises methylation, said method comprising:

a) determining the methyltransferase status of said subject; and

b) correlating said methyltransferase status with the ability of said subject to metabolize said compound, wherein said compound is predicted to be therapeutically effective if said methyltransferase status is enhanced in said subject, and wherein said compound is predicted not to be therapeutically effective if said methyltransferase status is reduced in said subject.

25. (Withdrawn) The method of claim 24, wherein said determining of said methyltransferase status comprises determining whether said subject comprises a variant *PNMT* nucleic acid.

26. (Withdrawn) The method of claim 25, wherein said variant *PNMT* nucleic acid comprises a non-synonymous single nucleotide polymorphism.

27. (Withdrawn) The method of claim 24, wherein said determining of said methyltransferase status comprises measuring methyltransferase activity in a biological sample from said subject.

28. (Withdrawn) The method of claim 27, wherein said methyltransferase activity is PNMT activity.

29. (Withdrawn) A method for predicting the therapeutic efficacy of a compound in a subject, wherein metabolism of said compound comprises methylation, said method comprising:

a) estimating the level of methyltransferase activity in said subject; and

b) correlating said level of methyltransferase activity with the ability of said subject to metabolize said compound, wherein said compound is predicted to be therapeutically effective if said level of methyltransferase activity is increased in said subject, and wherein said compound is predicted not to be therapeutically effective if said level of methyltransferase activity is reduced in said subject.

30. (Withdrawn) The method of claim 29, wherein said methyltransferase is PNMT.

31. (Withdrawn) The method of claim 30, wherein said methyltransferase activity is estimated in vitro in a biological sample from said subject.

32. (Withdrawn) The method of claim 29, wherein said level of methyltransferase activity in said subject is estimated by determining whether said subject comprises a variant *PNMT* nucleic acid.

33. (Withdrawn) The method of claim 32, wherein said variant *PNMT* nucleic acid comprises a non-synonymous single nucleotide polymorphism.

34-37. (Canceled)

38. (New) The isolated nucleic acid molecule of claim 1, wherein said isolated nucleic acid molecule is from 10 to 100 nucleotides in length.

39. (New) The isolated nucleic acid of molecule of claim 1, wherein said isolated nucleic acid molecule is from 20 to 50 nucleotides in length.

40. (New) A vector comprising the nucleic acid molecule of claim 1.

41. (New) The vector of claim 40, wherein said nucleic acid molecule is from 20 to 50 nucleotides in length.